NHS NORTHERN AND YORKSHIRE

REGIONAL DRUG AND THERAPEUTICS CENTRE

OCTREOTIDE

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CONTENTS

SUMMARY

- Octreotide is a long acting analogue of somatostatin, a hormone responsible for exerting endocrine control over many internal systems, including the gastro-intestinal tract.
- It is currently licensed in the UK for the treatment of acromegaly and rare gastro-enteropancreatic (GEP) tumours (e.g., carcinoid syndrome, VIPoma and glucagonoma). The overall incidence of all of these conditions in the Northern and Yorkshire region is probably less than 140 patients per year. It is also licensed for the prevention of complications following pancreatic surgery. However, there is considerable interest in the use of somatostatin analogues in a wide range of unlicensed indications.
- In acromegaly octreotide is more effective than bromocriptine at reducing growth hormone (GH) levels and normalising insulin-like growth factor-1 (IGF-1) levels.
- In patients with GEP tumours, octreotide may provide valuable symptom control. Treatment should on the basis of a one week therapeutic trial and withdrawn if there is no evidence of clinical benefit.
- There is some supporting evidence for octreotide in prophylaxis of complications in pancreatic surgery. It is reasonable to consider its use in patients at particular risk of complications.
- Octreotide is at least as effective as vasoconstrictors in the management of oesophageal variceal bleeding (*unlicensed indication*) and is better tolerated. In particular, it may have a role in early management, until invasive therapy is available, and as a long term adjuvant to sclerotherapy, where the incidence of re-bleeding and mortality is reduced compared with sclerotherapy alone.
- There is some supporting evidence for the use of octreotide in AIDS-related diarrhoea, pain management in chronic pancreatitis, acute pancreatitis, pancreatic ascites, and dumping syndrome (*unlicensed indications*). These approaches should currently be considered experimental.
- There is only limited evidence to support the use of octreotide in the prevention of pancreatitis following ERCP, short bowel syndrome, upper gastro-intestinal (GI) bleeding, advanced GI cancers, or chemotherapy-related diarrhoea (*all unlicensed indications*). Treatment with octreotide cannot currently be recommended for these conditions.
- Octreotide is generally well tolerated. Gastro-intestinal disturbances are common but usually resolve within 14 days of continuing therapy. However, long term use may be associated with biliary stasis and gallstone formation.
- Treatment with octreotide should be initiated by an appropriate specialist, usually an endocrinologist or gastro-intestinal physician or surgeon. For licensed indicati ns where ther is objective evidence of ben fit and where

a maintenance dose has been reached, it may be appropriate to transfer prescribing responsibility to GPs, with their prior and informed consent.

- Octreotide therapy is expensive. The annual cost of treatment with octreotide in a 70 kg adult is usually between £6 000 and £12 000, depending on dose. The total cost of primary care prescribing of octreotide in the Northern and Yorkshire region in 1998/99 was £697 300, an increase of 14.5% compared with 1996/97.
- For many indications the optimum dose and duration of treatment has yet to be determined. Octreotide is usually administered thrice daily by subcutaneous injection or intravenous infusion; a long acting depot preparation is also available.
- An intramuscular depot preparation of octreotide has been developed and is licensed for the treatment of acromegaly and symptoms associated with gastro-enteropancreatic tumours. It appears to be as effective as subcutaneous octreotide in patients who have previously responded to octreotide.
- Lanreotide is a recently launched long acting somatostatin analogue which is licensed for the treatment of acromegaly and symptoms associated with neuro-endocrine tumours (especially carcinoid syndrome). Limited evidence suggests that lanreotide is of similar effectiveness to octreotide.

BACKGROUND

Octreotide is a synthetic analogue of somatostatin, a regulatory hormone involved in many physiological functions. Endogenous somatostatin is very short acting (biological half-life three minutes); octreotide was developed to offer a longer duration of action (half-life 113 minutes). In practice, in most cases, this allows it to be administered by intermittent subcutaneous injection rather than as a continuous intravenous or subcutaneous infusion.

Octreotide has three current licensed indications in the UK: acromegaly, gastro-enteropancreatic tumours, and prevention of complications following pancreatic surgery. However, it has been investigated in the management of a very wide range of other conditions. This report assesses its place in treatment in both licensed and unlicensed indications and, in addition, considers the framework within which octreotide should be prescribed.

Implications of licensing status

Marketing authorisation is granted by the UK Licensing Authority only after careful consideration of evidence of quality, efficacy and safety. The terms of the licence may limit the drug's clinical indications, dose or duration of treatment. Doctors may prescribe unlicensed preparations, or licensed products for unlicensed indications, but must accept full responsibility for clinical outcomes, including adverse events. Doctors who prescribe or authorities that purchase treatment with unlicensed octreotide should consider the implications carefully. **GPs should, as a rule, avoid prescribing for unlicensed indications.**

LICENSED INDICATIONS FOR OCTREOTIDE

ACROMEGALY

Acromegaly is a rare pituitary disorder, with an estimated prevalence of between 38 and 69 per million population and annual incidence between 3 and 6 per million.[1,2,3,4] In Northern and Yorkshire region, there may be up to 450 patients with acromegaly. It can occur at any age but most patients present between the age of 40 and 50 years. In almost all cases acromegaly is caused by a somatotropinoma, a growth hormone (GH) secreting primary pituitary adenoma. Signs and symptoms develop slowly thus diagnosis may be delayed for many years. Acromegaly is characterised by coarsening of the facial features, increase in soft tissue mass, greasy skin, and deep voice. Systemic involvement is progressive and includes cardiomyopathy, respiratory problems, headache, hypertension, visual field defects, impaired glucose tolerance (which may give rise to frank diabetes mellitus), and arthralgia. Failure to suppress GH to less than 1 mU/l following an oral glucose tolerance test may indicate a diagnosis of acromegaly. Patients with acromegaly have a reduced life expectancy and about half of untreated patients will die before the age of 50 years.[3]

The aim of treatment is to normalise GH levels (mean value <5 mU/l). Cure is generally defined as a normalisation of the blood levels of insulin-like growth factor-1 (IGF-1). There are few studies which have evaluated the mortality benefit of reducing GH levels; in an audit of 79 patients with acromegaly, patients with GH levels less than 10 mU/l had twice the number of deaths expected while those with levels less than 5 mU/l had a survival rate similar to the general population.[5]

Rajasoorya et al described the outcome of 151 patients who were followed up for a median of 11 years.[6] There was a statistically significant association between mortality and high last recorded GH level.

Surgical removal of the pituitary tumour is the treatment option of first choice and reduces GH levels to less than 10 mU/L in at least 60% of patients, although about half of these will still have high IGF-1 levels. In a series of 79 patients, post-surgery basal GH was ≤2 mU/l in 21%, <5 in 59.2%, <10 in 73.6% and <20 in 90.8%.[7] Patients with a post operative GH level ≤2 mU/l were very unlikely to relapse, and more than half of the patients with post operative levels <10 mU/l did not require further treatment at late assessment (the mean follow-up period was 85.5 months). Radiation therapy may be given to patients whose plasma GH or IGF-1 levels remain high following surgery, but, GH levels may take many years to decline.

If these approaches fail to reduce GH levels sufficiently, or pending an assessment of the effect of radiotherapy either bromocriptine or octreotide[a] may be used to reduce GH secretion.

Clinical studies (mostly open) suggest that although bromocriptine may produce clinical improvement, suppression of GH levels to less than 10 mU/l and tumour shrinkage occurs in only a minority (20%) of patients.[3,8]

A large number of published studies have assessed the effect of octreotide in acromegaly. This review is necessarily restricted only to key trials.

Controlled studies have shown that, in the short term, octreotide suppresses GH levels to <10 mU/l in around 50% of patients, and achieves normalisation of IGF-1 levels in between 46% and 68%.[9,10] The extent of GH suppression did not appear to be dose-related.

In an open assessment of longer term efficacy and safety, Newman et al followed 103 patients for up to three years in whom the mean daily dose, after dose titration, was 801 mcg.[11] Seventy patients had a history of previous pituitary surgery (performed at least 21 months previously); 28 patients had also been treated with radiotherapy; six patients had received radiotherapy without surgery. After three months of treatment, GH levels were 10 mU/l or less in 65% of patients and 4 mU/l or less in 40% of patients. The mean GH level was significantly less than pre-treatment baseline throughout ($p<0.001$). Eighty-seven patients (84%) had elevated IGF-1 concentrations at the start of the study of which 49 patients (56%) had been reduced to within normal limits after three months of treatment and remained at this level throughout the study period. Normal IGF-1 levels were less likely to be achieved in patients who had high initial GH levels ($p<0.001$). In general, dose increments above 800 mcg daily in 31 patients did not lead to further reductions in GH or IGF-1 levels. Clinical symptoms such as headache, joint pain, and fatigue were also significantly improved throughout the study compared with baseline scores ($p<0.001$). The adverse effects reported most commonly were diarrhoea, abdominal discomfort, loose stools and nausea but these tended to be reported less

[a] Octreotide is licensed in acromegaly for: the short-term management of patients prior to surgery or in those who are not controlled by surgery, dopamine agonist treatment (such as bromocriptine) or radiotherapy; the period during which radiotherapy exerts its effect; and in patients for whom surgery is inappropriate.

often as the treatment continued; five patients withdrew from the trial due to adverse effects. Prior to treatment 102 patients had normal gallbladder ultrasound scans but after three years of treatment 24 of these had developed gallstones, while a further 21 had developed sludge only. Most of these patients were asymptomatic and there were no cases of acute cholecystitis. There was no evidence of a dose relationship in the development of gallstones or sludge.

There have been no double blind, randomised controlled trials directly comparing bromocriptine with octreotide. Several trials have compared both drugs in unblinded trials of varying duration. A review of published trials concluded that although the improvement in symptoms is similar with both drugs, octreotide shrinks somatotropinomas in about 60% of cases, compared with 10-20% with bromocriptine, and is more effective in reducing GH and IGF-1 levels than bromocriptine.[8]

Short term treatment prior to surgery

Stenenaert and Beckers reported on 172 patients with acromegaly, 64 of whom were given octreotide for varying periods prior to surgery. Fourteen received short term treatment of between three and six weeks, 50 patients had longer term treatment of between three and 39 months, and the remainder had no drug treatment prior to surgery.[12] Prior to treatment 81 patients had adenomas extending outside the sellar compared with 91 who had intrasellar adenomas. Patients who received octreotide showed a reduction in GH level of at least 50%; IGF-1 levels were reduced to within normal limits in 7 of 14 patients after short term treatment and 31 of 50 patients on longer term treatment. All octreotide treated patients had a reduction in pituitary size, which was proportional to the dose and duration of treatment. After surgery there was a higher incidence of remission only in pre-treated patients with intrasellar adenomas ($p<0.05$); there was no similar advantage where adenomas extended outside the sellar.

GASTRO-ENTEROPANCREATIC TUMOURS

Gastro-enteropancreatic (GEP) tumours are a rare and diverse group of malignancies, with an incidence of about 15 per million population, or about 100 new cases per year in Northern and Yorkshire region. Octreotide inhibits the inappropriate secretion of peptides by GEP tumours, and is used to treat related symptoms.

Carcinoid syndrome usually arises as a result of a midgut tumour (with hepatic metastases) which secretes serotonin (5-HT) and vaso-active peptides. Patients typically present with flushing, bronchospasm, and diarrhoea. Although the flushing lasts only a few minutes in the early stages of disease, it becomes almost continuous as disease progression occurs. Diarrhoea is often severe. The annual incidence of carcinoid syndrome is estimated at 1 per 0.5M population, which would result in about 13 new cases per year in Northern and Yorkshire region.[3]

The aim of therapy in carcinoid syndrome is to achieve symptom control; median survival from diagnosis is approximately five years although some patients survive for up to 20 years. Case studies have shown that octreotide can reduce flushing and diarrhoea in many patients.[13] One randomised, controlled study has been

published; ten patients with carcinoid syndrome and one patient with a glucagonoma, none of whom had previously received octreotide, were treated for four weeks with octreotide 100 mcg twice daily or placebo.[14] The primary outcome measure of efficacy was the level of urinary 5-HIAA (a metabolite of serotonin), which was significantly reduced after octreotide treatment, compared with placebo ($p=0.007$). The frequency of flushing ($p=0.01$) and diarrhoea ($p=0.02$) was also reduced by octreotide. The investigators also assessed quality of life using the General Health Questionnaire (GHQ-30) and Psychological Adjustment of Illness Scale (PAIS). GHQ-30 scores did not change during the trial and only two sub-sections (ability to relate socially and psychosocial distress) of the PAIS assessment were significantly improved ($p<0.05$) following octreotide therapy. Two patients withdrew from the study, one due to octreotide-related adverse effects (severe facial, leg and arm oedema with dyspnoea which recurred upon octreotide rechallenge). Tumour size was not recorded. There are infrequent reports that octreotide can cause tumour shrinkage.[15,16]

Glucagonomas are very rare, with an incidence of 1 in 20 million per year. About 70% of patients have metastatic disease at the time of presentation. Glucagonomas secrete various forms of glucagon and other peptides causing abdominal pain, diabetes, diarrhoea, and a necrolytic migratory rash. Octreotide appears to be useful in the management of the rash but the effect on other symptoms is variable.[3,13]

VIPomas are extremely rare and typically present with large volume watery diarrhoea due to the increased secretion of VIP (vaso-active intestinal peptide). Surgical resection is the treatment of choice but about 50% of patients have metastatic disease at presentation. Octreotide provides palliation of symptoms but is not curative. Between 80% and 90% of patients show a response to octreotide therapy and VIP levels decline in 60%. Over time there may be a loss of sensitivity to octreotide and doses of up to 1 mg/day may be required.[13]

PROPHYLAXIS OF COMPLICATIONS IN PANCREATIC SURGERY

Pancreatic surgery carries a high risk of morbidity (30-40%) and mortality (3-10%) due to exocrine pancreatic secretion.[17] Several randomised, double blind trials have investigated the prophylactic use of octreotide in pancreatic surgery.

Buchler et al stratified 246 patients undergoing pancreatic resection according to high risk and low risk status[b].[17] Each group was randomised separately to seven days therapy with either octreotide (100 mcg thrice daily) or placebo. The overall complication rate was significantly higher in the placebo group (32% of octreotide group had one or more complications vs 55.4% in the placebo group, $p<0.005$). The single most common complication was pancreatic fistula. The rate of complications was also lower amongst the high risk patients treated with octreotide than for the high risk placebo group (38% vs 65%, $p<0.01$). There was a similar but non-significant trend in the low risk group. The most commonly reported adverse event was pain on injection (25% octreotide, 21% placebo).

[b] Assigned according to relative difficulty in surgical technique: high risk status - those patients with pancreatic or periampullary tumours; low risk status - those with chronic pancreatitis

In a similar trial, 252 patients were randomised to octreotide (100 mcg thrice daily) or placebo for seven days.[18] Patients were pre-stratified according to risk status, as in the previous study. Overall morbidity was lower in the treatment group (15.6% vs 29.2%, p=0.01). Upon further analysis, the morbidity rate was found to be significantly lower in the low risk, active treatment group (p=0.05). The length of hospital stay did not differ between the groups. The authors reported that although the complication rate was consistently higher in the placebo group, there was substantial intercentre variability.

Following the encouraging results from these two trials, Freiss et al conducted a double blind investigation of octreotide in resection or pancreatic duct anastomosis in patients with chronic pancreatitis.[19] Two hundred and forty seven patients were randomised to receive either octreotide (100 mcg thrice daily) or placebo for eight days. The complication rate was significantly reduced in patients receiving octreotide (16.4% vs 29.6%, p<0.007). The frequency of fistula formation was significantly lower in the treatment group (9.8% vs 22.4%, p<0.05). The length of hospital stay was not significantly different between the two groups.

In a study designed to determine the incidence of pancreatic fistula formation after resection, 218 patients were randomised to receive octreotide (100 mcg thrice daily) or placebo for seven days.[20] The incidence of fistula formation was significantly lower in patients given octreotide (9.0% vs 19.6%, p<0.05) and the proportion of patients with one or more complications was also lower (21.6% vs 36.4%, p<0.05).

INDICATIONS FOR WHICH OCTREOTIDE IS NOT CURRENTLY LICENSED

OESOPHAGEAL VARICEAL BLEEDING

Oesophageal variceal bleeding, a complication of portal hypertension, is a medical emergency with a mortality rate of between 30% and 50%.[21] Following basic life support measures, a number of treatments may be used including vaso-active drugs, balloon tamponade, endoscopic sclerotherapy, banding ligation, surgical transection and shunts, all of which aim to control haemorrhage.[3] Octreotide reduces portocollateral blood flow and lowers portal pressure. A number of studies have investigated its use in either the initial control of bleeding or in the prevention of bleeding recurrence.

Three randomised trials have compared octreotide with vaso-active drugs to control acute bleeding of oesophageal varices.

Huang et al randomised 41 patients with liver cirrhosis and bleeding oesophageal varices to octreotide (100mcg bolus followed by 25mcg/h infusion for 24 hours) or vasopressin (0.4 units/minute for 24 hours).[22] More patients (60% vs 33.3%) who received octreotide had complete control of haemostasis at 24 hours compared with the vasopressin group, but the difference was not statistically significant. The octreotide group did, however, have a significantly lower transfusion requirement. Octreotide tended to cause fewer side effects but the difference was not significant. Patients who received vasopressin had more severe side effects (abdominal pain, bradycardia, chest pain and ischaemic purpura), while those who received octreotide experienced abdominal fullness and nausea.

In a further study comparing octreotide with vasopressin, 48 patients were randomised to receive octreotide (100 mcg bolus followed by 25 mcg/h infusion for 24 hours) or vasopressin (0.4 units/minute for 24 hours), following a confirmed oesophageal bleed.[23] Initial control of bleeding was significantly better in the octreotide group but at 24 hours after treatment there was no significant difference. Mortality at 42 days was similar in both groups, although patients with early control of bleeding had a significantly lower rate of mortality (35% vs 78%, p=0.02) regardless of treatment. Patients receiving vasopressin experienced a higher incidence of adverse effects, none of which were serious.

Silvain et al randomised 87 patients to receive terlipressin plus glyceryl trinitrate therapy (2 mg terlipressin bolus followed by 1 mg bolus every four hours and 10 mg glyceryl trinitrate every 12 hours percutaneously both for 24 hours) or octreotide (25 mcg/h for 12 hours then 100 mcg subcutaneously at 12 hours and 18 hours).[24] All patients had endoscopically confirmed oesophageal variceal bleeding. Octreotide was at least as effective as terlipressin at controlling variceal bleeding; patients receiving octreotide required significantly fewer blood transfusions than the terlipressin group. Two patients receiving terlipressin had to withdraw because of severe side effects, one with fatal left ventricular failure and one with severe bradycardia. Two other patients who received terlipressin experienced bradycardia, one patient had tachycardia and one patient had hypertension. Seven patients in the octreotide group had moderate hypoglycaemia and two patients had transient diarrhoea.

A number of studies have assessed the use of octreotide in place of, or as an adjunct to invasive methods for control of bleeding. For example, 94 patients were randomly assigned to endoscopic ligation alone or ligation plus octreotide (50 mcg bolus during endoscopy followed by 50 mcg/hour infusion for an unspecified length of time).[25] There was no difference in the initial control of bleeding but significantly fewer patients receiving octreotide rebled (38% vs 9%, p=0.007). Only one patient in the octreotide group required balloon tamponade to achieve haemostasis compared with 10 patients who received ligation alone. There were fewer deaths in the group who received octreotide but the difference was not statistically significant.

Besson et al compared the effectiveness of emergency sclerotherapy with and without octreotide in patients with acute variceal bleeding.[26] One hundred and ninety nine patients underwent sclerotherapy and were then randomly assigned to receive octreotide (25 mcg/hour for 5 days) or placebo infusion. Significantly more patients receiving octreotide survived without rebleeding at five days (87% vs 71%, p=0.009) and octreotide treated patients also required significantly fewer transfusions. At 15 days after treatment mortality rates were the same in each group (12%).

Sung et al randomised 98 patients with bleeding oesophageal varices to octreotide infusion (50 mcg bolus followed by 50 mcg/hour infusion for 48 hours) or emergency sclerotherapy alone, both followed by elective sclerotherapy.[27] There was no difference between the groups in control of bleeding, bleeding recurrence in first 48 hours, use of balloon tamponade, duration of hospital stay, or mortality.

In a similar study, 150 patients with variceal bleeding were randomised to receive either emergency sclerotherapy alone or octreotide (50 mcg/h infusion for 48 hours), both followed by elective sclerotherapy.[21] There was no difference between the

groups in the control of bleeding and incidence of mortality at 48 hours. At 60 days follow-up there was a trend towards increased mortality in the octreotide group but this was not statistically significant (relative risk of dying at 60 days 1.91, 95% CI 0.97 to 3.78, p=0.06).

In a multicentre, double blind, placebo controlled trial Primignani et al randomised 58 patients to receive octreotide (100 mcg three times daily subcutaneously to day 29) or placebo injections, following emergency sclerotherapy.[28] All patients received elective sclerotherapy throughout the study. There was no difference between groups in the rebleeding rate (31% vs 34%) or bleeding-related mortality. One possible reason for this is that the intermittent administration of octreotide is unlikely to maintain a low portal pressure.

In the only randomised trial yet published of long term octreotide therapy for cirrhosis after variceal haemorrhage Jenkins et al randomised patients who had cirrhosis and variceal bleeding controlled by injection sclerotherapy.[29] Patients received either octreotide (50 mcg twice daily, n=16) or no treatment (n=16) for six months. Both groups continued to receive injection sclerotherapy until all oesophageal varices had been obliterated. Significantly fewer patients rebled in the treatment group during the six month study period (6.2% vs 43.8%, p=0.037); at the end of the trial there were no deaths in the octreotide group (0 vs 5, p<0.02); this survival advantage was maintained for a further 12 months. Four of the five deaths were due to recurrent bleeding. A limitation of this trial is that octreotide was compared with placebo rather than conventional pharmacological treatment of portal hypertension (beta-blockers or nitrates).

ACUTE PANCREATITIS

Acute pancreatitis is associated with high morbidity and mortality and at present there is no specific treatment.[30] Due to the nature of the disease, published studies of octreotide in acute pancreatitis are generally of limited power and poor methodology. For example, of 19 patients with varying severity of disease the first 10 acted as controls while the next nine received 250 mcg octreotide subcutaneously following diagnosis, followed by an intravenous infusion of 0.5 mcg/kg/h, until 24 hours after becoming pain free, up to a maximum treatment period of 10 days.[31] Efficacy was assessed by a series of prognostic indicators of which only some showed a significant improvement compared with controls (haemocrit, haemoglobin, serum calcium, serum albumin and fall in arterial oxygen saturation). However, individual prognostic indicators are of little value in assessing the severity of pancreatitis and are only surrogate endpoints. Patients who received octreotide had a significantly lower average consumption of pethidine, which was administered by nursing staff not involved in the study; the authors do not state whether they were blinded to treatment group assignation. There were no deaths during the study period, reflecting generally low Ranson and Glasgow scores assessed at trial entry (mean Ranson score 0.9, 0-3)[c].

[c] Ranson score - a grading system of 11 prognostic factors for patients with acute pancreatitis due to alcohol abuse or gallstones; Glasgow score - a scoring system of eight prognostic factors for patients with acute pancreatitis due to alcohol abuse or gallstones.[3]

In a randomised study of 38 patients with severe acute pancreatitis, those who received octreotide (100 mcg thrice daily for 14 days) had fewer septic complications compared with the control group (26% vs 74%, p=0.004).[32] There was also a lower incidence of adult respiratory distress syndrome (ARDS) but the difference did not reach statistical significance (37% vs 63%, p=0.1). The mean length of inpatient stay was also less than for the untreated patients (17.9 vs 34.1 days, p=0.02). Two patients in the treatment group died compared with six patients in the control group (p=0.11).

In a further trial, 39 patients with necrotising pancreatitis and pulmonary failure requiring ventilation were treated with octreotide 100 mcg intravenously three times a day for 10 days.[33] When compared with case matched controls (n=54), patients treated with octreotide had significantly lower mortality (26% vs 61%, p<0.01). In addition, significantly fewer treated patients developed ARDS or circulatory shock (p<0.05).

In a recent trial, 58 patients with moderate or severe acute pancreatitis were randomised to receive either octreotide infusion (40 mcg/h for five days) or placebo.[34] Mortality was similar in both groups (18% vs 20%), and the difference in complication rate, although higher in the octreotide group, did not reach statistical significance (36% vs 20%). Median hospital stay was 10 days in both groups.

The results of a larger, double blind, placebo controlled study in 300 patients are awaited.[35]

Acute pancreatitis also occurs in between 1% and 5% of patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) or after endoscopic sphincterotomy (EST). In four randomised trials of peri-operative octreotide or placebo, none found octreotide to confer an advantage over placebo in terms of reducing the incidence of pancreatitis, although the largest study showed that the octreotide did reduce the rate of amylase increase compared with placebo.[36,37,38,39] In one study the incidence of pancreatitis was increased, compared with placebo but episodes of pancreatitis in the treatment group appeared to be less severe than in the placebo group.[36]

AIDS-RELATED DIARRHOEA

Somatostatin prolongs gastro-intestinal transit time, reduces endogenous fluid secretion and increases intestinal absorption of water and electrolytes; octreotide has therefore been investigated as an antidiarrhoeal agent for secretory diarrhoeas.

AIDs-related diarrhoea is common, is poorly understood and medical treatment is often ineffective.

In an early open study, 51 patients with chronic uncontrolled AIDS-related diarrhoea were given octreotide 50 mcg thrice daily initially, increasing every 48 hours to 100, 250 then 500 mcg thrice daily, according to response.[40] After seven days at the titrated level, the dose was reduced and discontinued over four days. Patients were continued on any pre-study antidiarrhoeal medication. Twenty one patients (41%) had a complete or partial response[d] to octreotide therapy. When octreotide was

[d] Complete response - reduction in stool volume to less than 250 ml/day.

withdrawn, stool frequency increased to pre-treatment levels. Patients in whom there was no identifiable pathogen were more likely to respond to therapy (67% of responders vs 30% of non-responders, p<0.01). Faecal fat content was reported to be increased in all patients following octreotide therapy. Fifteen patients remained on octreotide for six months, none developed gallstones or acute cholecystitis.

In a small, randomised, placebo controlled study in 20 patients with large volume refractory diarrhoea, octreotide (100 mcg thrice daily increased every 72 hours to 300 mcg thrice daily) was compared with placebo plus high-dose loperamide and diphenoxylate therapy.[41] More patients in the octreotide group had a complete or partial response[d] compared with the control group (60% vs 20%, p<0.05).

In a larger, double blind, randomised study 124 patients with AIDS-related diarrhoea refractory to conventional therapy were randomised to receive octreotide (100 mcg thrice daily and increased by 300 mcg daily every seven days if there was an inadequate response to a maximum of 300 mcg thrice daily) or placebo for three weeks.[42] At the end of this period, patients were entered into an open-label treatment arm, to receive up to 500 mcg thrice daily. Response to therapy was defined as at least a 30% decrease in stool weight. During the controlled phase, there was no significant difference in response rate between the two treatment arms. After eight weeks of therapy at 500 mcg thrice daily, there was a mean decrease of 42.3% in stool weight (p<0.001) compared with the pre-octreotide baseline.

CHEMOTHERAPY-RELATED DIARRHOEA

Octreotide has also been evaluated in chemotherapy-induced diarrhoea; three small randomised trials have compared it with loperamide.

Forty-one patients receiving fluorouracil (and with a white cell count greater than 3000/μL to exclude infective diarrhoea) with four to nine stools per day were randomised to octreotide (100 mcg twice daily) or loperamide (4 mg initially, followed by 2 mg every six hours), for three days.[43] Diarrhoea resolved completely in 90% of the octreotide group compared with 15% of the loperamide group (p<0.005).

Forty patients with chemotherapy-induced diarrhoea were randomised to receive octreotide (500 mcg thrice daily) or loperamide (4mg thrice daily); therapy was continued until the diarrhoea stopped or until four days of treatment had been given.[44] The authors did not state whether an infective origin had been excluded. There was complete remission of diarrhoea in significantly more patients receiving octreotide, compared with those given loperamide (80% vs 30%, p<0.001).

Thirty-six patients with diarrhoea related to chemotherapy given for bone marrow transplant or treatment of leukaemia were randomised to receive octreotide (150 mcg intravenously over 24 hours and doubled every 48 hours if there was only a minimal response, to a maximum of 2.4mg) or loperamide (4 mg every six hours for 48 hours and continued if there was a response until the diarrhoea had stopped).[45] Patients with infective diarrhoea were excluded. One patient from the loperamide group and four from the octreotide group did not receive treatment in accordance

[d] Partial response - reduction in stool volume by 50% or more from initial value but greater than 250ml/day

with the trial protocol for the first 48 hours. When the results were analysed on an intention-to-treat basis, more patients receiving loperamide responded to treatment within 48 hours (86% vs 45%, p=0.033); when analysed by treatment, 92% of loperamide patients had a major response compared with 56% of the octreotide patients (p=0.05). With dose escalation (doses up to 600 mcg/24 hours), 78% of patients on octreotide eventually responded.

CHRONIC PANCREATITIS

Pain is the main clinical symptom of chronic pancreatitis and is often difficult to treat effectively. Approaches to treatment include analgesic drugs, pancreatic enzymes, nerve blocks and surgery.[46] The pain is thought to be due to an increase in intraductal pressure during pancreatic secretion and octreotide has been used as it inhibits pancreatic secretion. Several small trials have investigated the effectiveness of octreotide with varying degrees of success, perhaps related to the length of treatment time. In one trial, octreotide was given for only three days and there was no difference between active and placebo treatment. Other trials (available as abstracts only), where octreotide was given for four weeks showed that it reduced pain and analgesic use compared with placebo.[47,48,49]

DUMPING SYNDROME

The symptoms of dumping syndrome occur most commonly after a large or carbohydrate-rich meal and are thought to be related to rapid gastric emptying. Early dumping occurs within half an hour of a meal and causes abdominal distension, fainting, palpitations, sweating, tiredness, and occasionally diarrhoea. Late dumping is less common, usually occurs two hours after a meal and is accompanied by sweating, tachycardia, mental confusion, and syncope; it occurs in about half of patients who have undergone gastric surgery. A small proportion of patients (3-5%) fail to respond to dietary measures. Since octreotide delays gastric emptying, it has been studied in dumping syndrome in a few small trials.[50]

In a cross-over study Tulassey et al randomised eight patients to receive either octreotide (50 mcg) or placebo 15 minutes prior to ingestion of glucose.[51] Following placebo, all patients experienced typical symptoms of early dumping syndrome (palpitation, fainting, weakness, epigastric distress). After octreotide, three patients experienced nausea but all other symptoms were absent. The mean time taken to reach peak blood glucose levels was significantly longer in the octreotide group (30 minutes vs 90 minutes, p<0.001). Hypoglycaemia related to dumping developed in seven patients after placebo. Octreotide did not alter the increase in pulse rate, packed cell volume or plasma levels of VIP observed after glucose ingestion. In the placebo group, insulin and gastric inhibitory polypeptide levels were significantly raised (p<0.001) after glucose ingestion but remained unchanged with octreotide.

In a similar randomised cross-over study, ten patients with severe dumping syndrome received octreotide (100 mcg) or placebo 30 minutes prior to the test meal.[50] After the two day trial, all patients continued with octreotide (30-70 mcg) three or four times daily for between three and 15 months. Following placebo there was a significant increase in mean pulse rate (p<0.01), but not with octreotide. Octreotide also reduced the severity rating of the symptoms of dumping syndrome (p<0.001) including the two patients with late dumping symptoms. In these two

patients octreotide also prevented hypoglycaemia. The high plasma insulin levels seen during the placebo phase were also blocked by octreotide and the increase in plasma glucose was significantly higher in the octreotide group ($p<0.01$). There was no difference in VIP levels between groups. There was no difference between the two arms in gastric emptying time following a meal of scrambled eggs. Long term treatment with octreotide was associated with significant weight gain, stable fasting blood glucose levels and normal liver enzymes; seven patients who had previously been unemployed were able to resume work.

In a further randomised, double blind, cross-over trial, nine patients with severe symptoms of dumping syndrome were treated with octreotide (100 mcg) or placebo 30 minutes prior to a liquid meal.[52] There was a significant decrease in the number of patients experiencing dumping symptoms in the octreotide arm, compared with placebo (2 vs 9, $p<0.004$). The increase in pulse rate observed in the placebo arm was abolished in the octreotide arm ($p<0.005$). There was no difference in the increase in haemocrit value or plasma osmalility between the groups. Insulin levels increased significantly more in the placebo arm compared with octreotide ($p<0.05$).

ENTERIC FISTULAS

A few small studies, most of which were unblinded, have investigated the use of octreotide to reduce the output from enteric fistulas and speed up the time to spontaneous closure. For example, in a cross-over, single blind trial 14 patients with small bowel fistulas who had been treated for a minimum of seven days with parenteral nutrition received octreotide (225-300 mcg daily, in three divided doses) for two days followed by two days of placebo, or vice versa.[53] All patients then received octreotide until the fistula closed spontaneously or they had surgery. Octreotide significantly reduced fistula output (mean 828 ml/24 h on placebo and 247 ml/24 h after octreotide ($p<0.01$) in the group given placebo first and by 498 ml/24 h to 228 ml/24 h ($p=0.014$) in the group given octreotide first). The fistula closed spontaneously in 11/14 patients between two and ten days after starting octreotide (mean 4.5 days).

In the only published double blind, placebo controlled trial, 31 patients with a gastro-intestinal or pancreatic fistula of less than seven days duration were randomised to receive octreotide (300 mcg daily in three divided doses) or placebo, together with parenteral nutrition, either until the fistula closed spontaneously or after a maximum of 19 days of therapy.[54] There was no difference in fistula output, number of closures or time to closure between the groups.

GASTRO-INTESTINAL CANCERS

Somatostatin is an antiproliferative hormone and has been shown to inhibit proliferation of cells in normal and neoplastic mucosa in the stomach, pancreas and colon-rectum. Two studies have evaluated the efficacy of octreotide in patients with advanced gastro-intestinal cancer.

Cascinu et al compared octreotide or supportive treatment in 107 patients with advanced stomach, pancreas or colorectal cancer unresponsive to chemotherapy.[55] After stratification by performance status and primary tumour, patients were randomised to receive octreotide (200 mcg thrice daily subcutaneously for five days

each week) or to supportive care. Although no patients had an objective response to octreotide therapy, significantly more patients given octreotide had stable disease[e] compared with the control group (45% vs 15%, p<0.001). There was also a significant increase in survival time in the octreotide group compared with controls (median 20 weeks vs 11 weeks p<0.001), which appeared to be independent of performance status or the type of primary tumour. Twenty patients (36%) on octreotide experienced asymptomatic hyperglycaemia, 10 (18%) had mild steatorrhea and three had abdominal cramps which lasted only a few days.

In a second randomised trial, the first 91 patients with unresectable or metastatic colon cancer were randomised to receive octreotide (150 mcg thrice daily) or no treatment, the remaining patients were randomised to active treatment or matched placebo injections.[56] A total of 131 patients were entered in the octreotide and 129 patients in the untreated/placebo arm. Neither the median time to disease progression nor survival time were significantly different between the groups.

The discovery that patients with hepatocellular carcinoma (HCC) had somatostatin receptors present on liver biopsy lead Kouroumalis et al to investigate the role of octreotide in this condition.[57] Fifty eight patients with advanced HCC were randomised to receive either octreotide (250 mcg twice daily) continued until death or no treatment. Octreotide treated patients had a significantly prolonged median survival compared with untreated patients (13 months vs 4 months, p=0.002); 75% of treated patients were still alive at six months compared with 37%, and at 12 months 56% were still alive compared with 13%.

PANCREATIC ASCITES

Pancreatic ascites is caused by a pancreatic fistula and conventional treatment is to either rest the pancreas by giving total parenteral nutrition (TPN) until the fistula has healed or perform early surgery. Octreotide has been investigated in pancreatic fistula as it inhibits pancreatic secretion. In one series, 23 patients with pancreatic ascites or effusion were treated with TPN, ten of whom responded. Octreotide (100 mcg thrice daily) was added to therapy in five patients, all of whom responded. In the other eight patients, six had surgery, one died and one declined all further intervention.[58]

In a further series of ten patients with pancreatic ascites, octreotide (100 mcg thrice daily), caused complete resolution in nine patients and partial resolution in one. The mean time to resolution of ascites was 22 days.[59]

SHORT BOWEL SYNDROME

Octreotide has been investigated in the treatment of short bowel syndrome-related diarrhoea in a number of small cross-over trials, where it appeared to reduce stomal output in some patients and to increase water and electrolyte absorption.[60]

Resection of the terminal ileum is sometimes associated with diarrhoea due to the reduced surface area available for absorption, increased secretion of intestinal fluid

[e] Where neither a 50% decrease in tumour size can be established nor a 25% increase in tumour size demonstrated.

and increased gastric motility. In a randomised, placebo controlled, cross-over trial investigating the use of octreotide in ileostomy-associated diarrhoea, Kusuhara et al treated 12 patients.[61] After a control week, patients were given either placebo or octreotide injections (100 mcg thrice daily) for five days. Octreotide reduced ileostomy output from a mean of 997 g/day to 736 g/day ($p<0.05$), while placebo had no effect.

UPPER GASTRO-INTESTINAL BLEEDING

In a randomised, placebo controlled trial, 241 patients with moderate to severe peptic ulceration with active bleeding (confirmed by endoscopy) requiring blood transfusions or plasma expanders were randomised to receive octreotide (50 mcg bolus followed by an intravenous infusion of 25 mcg/hour for 48 hours followed by 100 mcg subcutaneously every eight hours for 3 days) or placebo.[62] There was no significant difference between the groups in the cessation of bleeding or rebleeding during the trial period (69.6% vs 70.6% for octreotide and placebo, respectively).

OTHER USES

Octreotide has been advocated for the treatment of nausea and vomiting in palliative care as it stimulates water and electrolyte absorption and inhibits water secretion in the small bowel.[63] In an open, non-comparative trial, 24 terminally ill patients, with intestinal obstruction giving rise to vomiting which did not respond to a combination of anti-emetics, steroids and/or naso-gastric drainage, and who were not suitable for surgery, were treated with octreotide (100-150 mcg daily and increased until control of vomiting was achieved).[64] Fourteen patients achieved a complete response (no nausea and vomiting), and four patients had a partial response; the response was maintained until death in 16 patients. The median initial dosage required to control vomiting was 300 mcg daily and the dose was gradually reduced to 150 mcg daily in six patients.

Octreotide has been used to successfully treat a non-diabetic patient with severe, refractory, sulphonylurea-induced hypoglycaemia.[65]

ADVERSE EFFECTS

The most common adverse effects associated with octreotide are those which affect the gastro-intestinal system; nausea, abdominal cramps, diarrhoea, and flatulence are common at the start therapy in about half of all patients but usually subside within two weeks. Steatorrhoea can occur, which may lead to nutritional deficiency.

Treatment for more than one month is associated with an increased risk of biliary stasis which may lead to gallstone formation, which is usually asymptomatic. The development of gallstones does not appear to be dose-related but may be related to duration of treatment.[11,66]

Glucose metabolism may be impaired because octreotide inhibits insulin release. However, as octreotide also slows carbohydrate absorption and inhibits the secretion of glucagon and GH, treatment-related hyperglycaemia is rare unless there is concomitant liver disease or insufficient lowering of GH.

Pain, burning and stinging at the site of injection may occur. These effects may be minimised by allowing the solution to reach room temperature prior to injection.

DOSAGE, ADMINISTRATION AND COST

Octreotide (Sandostatin®, Novartis) is usually given by subcutaneous injection. It is available in ampoules and multidose vials. The table below gives details of the doses and costs of currently licensed indications.

Indication	Dose	Annual Cost (£)
Acromegaly	0.1-0.2 mg thrice daily	6 000-12 000
GEP tumours	0.05 mg daily-0.2 mg thrice daily	1 000-12 000
Prophylaxis in pancreatic surgery	0.1 mg thrice daily for 7 days	115 (single course)

Source: MIMS June 1999

Treatment with octreotide is relatively expensive. In certain licensed indications such as carcinoid and VIPoma, much higher, unlicensed doses have been used, incurring correspondingly higher costs (up to £20 000 per year). There is no published evidence of the cost-effectiveness of octreotide.

In Northern and Yorkshire region the primary care prescribing cost of octreotide in 1998/99 was £697 300, an increase of 14.5% compared with 1996/97, and with substantial variation between individual health authorities (appendix 3). No recent hospital usage information is available but based on hospital purchase data in 1995/96 in the Northern sector of the region, secondary care expenditure is likely to be in excess of that in primary care.

PLACE IN TREATMENT

LICENSED INDICATIONS

In **acromegaly** octreotide is more effective than bromocriptine at reducing GH levels and in normalising IGF-1 levels. However, there have been no prospective, randomised trials showing that the excess mortality associated with high GH levels can be reduced with octreotide treatment. Long term treatment is associated with biliary stasis and gallstone formation in some patients. It would seem reasonable to treat those patients who meet the criteria in the current UK licence (see p.6).

Gastro-enteropancreatic tumours are very rare and therefore there are few randomised, controlled trials. However, small controlled studies and case reports indicate that octreotide is effective in symptom control in carcinoid syndrome. It is therefore appropriate to offer symptomatic patients a trial of therapy with octreotide. The manufacturers recommend that patients with carcinoid syndrome should receive initial treatment for one week; if there is no response then treatment should be withdrawn.

Treatment with octreotide reduces the rate of post operative complications following **pancreatic surgery**. It is reasonable to consider use in patients at particular risk of complications.

UNLICENSED INDICATIONS

The studies reviewed to date indicate that octreotide is at least as effective as other vaso constrictors in the initial management of **oesophageal variceal bleeding** and has fewer side effects. The use of octreotide in combination with endoscopic ligation or sclerotherapy is not supported by the available evidence although it might be useful in the early management of acute bleeding until invasive therapy is available. However, octreotide, used as a long term adjuvant to sclerotherapy, appears to reduce the incidence of rebleeding and subsequently mortality, although this approach has not been compared with other drug therapies such as nitrates or beta-adrenergic antagonists.

In severe **acute pancreatitis**, octreotide may reduce complication rates and hospital stay. At present, a reduction in mortality has not been demonstrated. Specialist opinion is that there is, at present, no proven role for octreotide in this indication.

There is conflicting evidence about the efficacy of octreotide in the treatment of **AIDS-related diarrhoea,** which follows an unpredictable course, and may remit spontaneously. In one trial, over one-third of patients responded to placebo.

There is conflicting evidence to support the use of octreotide in the treatment of pain in **chronic pancreatitis**. If octreotide is used it should be reserved for severe cases which have failed to respond to conventional therapy.

Early results in very small trials suggest that octreotide may be effective in selected patients with **dumping syndrome** who are refractory to dietary manipulation. However, longer term, controlled trials are required to establish its eventual place in treatment. For patients who have failed to respond to other therapy options, a short term trial of octreotide may be justified.

There is insufficient evidence to support the use of octreotide in the treatment of **enteric fistulas** of recent onset or in stable fistulas in patients who have had previous treatment with parenteral nutrition. However, anecdotal reports suggest that continuous infusions of octreotide may be extremely useful in some patients.

There is little evidence that octreotide is effective in controlling nausea and vomiting due to intestinal obstruction in **palliative care**. However, its use may be considered if a patient has failed to respond to combination anti-emetics, steroids or naso gastric drainage and in whom palliative surgery is not an option.

There is insufficient current evidence to currently support the use of octreotide in **prevention of pancreatitis following ERCP, short bowel syndrome, upper gastro-intestinal bleeding** (other than from varices), **advanced GI cancers or chemotherapy-related diarrhoea**.

ARRANGEMENTS FOR PRESCRIBING

Octreotide should be initiated only by appropriate hospital specialists, usually endocrinologists or gastro-intestinal physicians or surgeons. For longer term use, initial treatment should be prescribed by hospitals within the framework of purchaser-provider agreements which might include prescribing virement schemes. In acromegaly and GEP tumours, it may be appropriate to transfer prescribing responsibility to GPs where the treatment has not already been provided for in

clinical agreements. This should be done with GPs' prior informed consent and: where there is objective evidence of continued benefit; where a maintenance dose has been established, and where early, well recognised adverse effects have been identified and managed appropriately. As with all such transferring of prescribing responsibility, local arrangements for the shared care of patients should be explicit. GPs should, as a rule, not be asked to prescribe octreotide for unlicensed indications.

OTHER DEVELOPMENTS

A long acting release formulation of octreotide (Sandostatin LAR®, Novartis) has been developed for the treatment of acromegaly. It was licensed in the UK in April 1998 for patients who are already stabilised on octreotide and in whom surgery, radiotherapy or dopamine agonist therapy is inappropriate or ineffective, or until radiotherapy becomes fully effective. It allows the drug to be administered as a monthly intramuscular injection. Trials have demonstrated that octreotide-LAR is at least as effective as subcutaneous octreotide in patients who have previously responded to octreotide therapy. Reduction of GH levels to <5 mU/l occurred in between 39% and 79% of patients in trials and in three trials, IGF-1 levels were reduced to normal in the majority of patients. In a recently published trial, four patients were treated for 12 months and eight patients were treated for 36 months with long acting octreotide.[67] At both 12 months and 36 months 50% of patients had a GH level <5 mU/l and IGF-1 was normalised in 60% of patients at one year and 75% of patients at three years. Two patients developed asymptomatic gallbladder sludge and one patient withdrew at 6 months because of gastro-intestinal symptoms. The side effect profile appears to be similar to that of the subcutaneous preparation; mild to moderate pain at the site of injection occurred in 28% and 45% of patients in two clinical trials.[68] It is also licensed for the treatment of symptoms associated with GEP tumours in patients who have previously been stabilised on subcutaneous octreotide. The licensed dose is initially 20 mg every four weeks and may be increase if necessary to 30 mg every four weeks. At a dose of 20 mg every four weeks the annual cost is £11 050.

Slow-release lanreotide (Somatuline®, Ipsen Ltd) was launched in the UK in May 1998 for the treatment of acromegaly when the levels of growth hormone remain abnormal after surgery or radiotherapy and for the symptoms associated with neuro-endocrine tumours, especially carcinoid syndrome. Lanreotide is a somatostatin analogue with actions similar to those of octreotide. Various trials have examined the efficacy of slow-release lanreotide in patients with acromegaly. In one trial of 22 patients mean GH levels were 10 mU/l or less in 68% and 5 mU/l or less in 27% of patients at six months, remaining unchanged during one to three year follow-up; IGF-1 levels were within normal range in 63% of patients.[69] Side effects included GI problems (e.g., nausea, mild abdominal pain) which occurred during 48 hours after injection in 13 patients, gallstones developed in 4 (18%) of patients. In a larger trial involving 57 patients mean GH levels were less than 10 mU/l in 85% and 4 mU/l or less in 66% of patients after six months and IGF-1 levels were within normal range for 38%.[70] In a trial of 39 patients with carcinoid syndrome, flushing and diarrhoea episodes were significantly reduced after one month's treatment; at six months the number of patients with at least a 50% decrease in flushing and diarrhoea episodes

compared with baseline was 53% and 59% respectively.[71] A quarter of patients experienced mild pain or erythema at the injection site and two patients developed gallstones after six months of treatment. At the licensed dose of 30 mg every two weeks, the annual cost is £9 100.

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APPENDIX 1. SUMMARY OF EFFICACY OF OCTREOTIDE IN THE TREATMENT OF UNLICENSED INDICATIONS.

Category	Condition
Efficacy and safety confirmed in controlled trial(s)	Variceal bleeding - superior and safer to other vasoconstrictors
Possibly effective but insufficient evidence at present	AIDs-related diarrhoea
	Acute pancreatitis
	Dumping syndrome
	Long term treatment of variceal bleeding, although no comparative data available
	Management of pain in chronic pancreatitis
	Pancreatic ascites
Inadequate evidence of efficacy and safety at present	Adjuvant therapy for the management of variceal bleeding
	Chemotherapy-related diarrhoea
	Enteric fistulas
	Gastro-intestinal cancers
	Prevention of pancreatitis in ERCP
	Short bowel syndrome
	Upper gastro-intestinal bleeding

APPENDIX 2. SUMMARY OF TRIALS

The published literature on octreotide is large and diverse, ranging from case studies to randomised controlled trials (RCTs). Only selected studies are included here. In addition, many studies are complex in terms of patient selection and outcome measures; for brevity, only summary information is provided here.

Key : MC – multicentre; SC -single centre; DB - double-blind; O –open; PC - placebo-controlled; R – randomised; CO - cross-over; PL - parallel groups; NS - not significant; HCC - hepatocellular carcinoma; EVS - endoscopic variceal schlerotherapy; VT - ventricular tachyarrythmias

ACROMEGALY

Reference	Design	Intervention	No. of patients	Outcome measures	Results	Adverse events
Vance et al 1991[9]	MC, O	Octreotide, mean dose 351mcg/d for 34.9±3 weeks	189	GH, IGF-1 levels	Pretreatment GH = 39.4mcg/L, post-treatment=12.2mcg/L, p<0.0001 and <5mcg/L in 45% of 182 patients. IGF-1 decreased to <2U/ml in 46% of 99 patients	
				Improvement in signs & symptoms	Response rate - 88%	
				Side effects	37% experienced S/E (usually <1 week), 8 patients had gallstones	
Ezzat et al 1992[10]	MC, R, DB, C	Octreotide 100mcg thrice daily for 4 weeks	60	GH at 4 weeks	GH level reduced from a mean of 39±11 to 9±2mcg/L, p<0.001	10% vs 13% (low vs high dose octreotide) had diarrhoea, 10% and 14% had biliary sludge and 6% and 18% had cholelithiasis
		Placebo injection for 4 weeks	55	IGF-1 at 4 weeks	IGF-1 level reduced from a mean of 5100±400U/L to 2400±400U/L, p<0.001	
		Then		GH at 6 months	53% and 49% of patients had GH levels<5mcg/L	
		Octreotide 100mcg thrice daily for 6 months	50			
		Octreotide 250mcg thrice daily for 6 months	54	IGF-1 at 6 months	68% and 55% of patients had normal IGF-1 levels	
				Improvement in clinical symptoms	Reduction in clinical symptoms in 2/3 of patients	
Newman et al, 1995[11]	MC, O	Octreotide 100mcg thrice daily and increased if necessary to 500mcg thrice daily for a mean of 30 months	103	GH	Mean level 30.9mcg/L pre-treatment fell to 5.7mcg/L, p<0.001.	
				IGF-1	Reduced to within normal levels for > 50% of treatment visits in 64% of patients	
				Adverse effects	GI side effects reported, resolved within 3 months. 23.5% developed gallstones and 21 patients developed sludge.	

GEP TUMOURS

Reference	Design	Intervention	No. of patients	Outcome measures	Results	Adverse events
Jacobsen et al, 1995[14]	DB, PC, CO	Octreotide 200mcg/d for 4 weeks Placebo for 4 weeks	11	1. Mean no. of flushing episodes/week 2. Mean no. of diarrhoea episodes/week 3. Quality of life (GHQ and PAIS questionnaires) 4. 5-HIAA urinary excretion	1. 20 vs 32, p=0.01 2. 8 vs 11, p=0.02 3. No change in GHQ score; significant improvement in ability to relate socially and psychosocial adjustment 4. Significantly reduced by octreotide (p=0.007)	Allergic reaction to octreotide (1), severe nausea (1), headache, chest pain, abdominal discomfort, anxiety
Arnold et al, 1996[15]	O	Octreotide 50mcg-500mcg tds	103	Tumour response in 52 patients with progression before treatment & 13 patients with stable disease Hormonal response in 48 patients with carcinoid syndrome	No tumour regression, 14/52 patients had stabilisation of disease at 3 months 64% had improvement in symptom control, 5-HIAA decreased by >50% in 33% of 39 patients	Steatorrhoea 3/28), gall stones (2/96), diarrhoea (34/96), pain at injection site (27/96), vomiting (11/96), hyperglycaemia (3/80)
Di Bartolomeo et al, 1996[16]	O	Octreotide 500 mcg tds	23	Tumour regression	2 (3%) patients with carcinoid showed objective response, 1 from each dose group	Steatorrhea (2), cholelithiasis (2) after 5 and 7 months
		Octreotide 1mg tds Both continued until tumour progression	35	Symptom response 5-HIAA urinary excretion	Of 15 patients with carcinoid syndrome 6 (40%) had complete reduction and 5 (33%) had partial response Normalised in 4 patients out of a total of 15 patients with abnormal baseline levels	

PANCREATIC SURGERY PROPHYLAXIS

Reference	Design	Intervention	No. of patients	Outcome measures	Results	Adverse events
Buchler et al 1992[17]	MC, R, DB, PC,PL	Octreotide 100mcg thrice daily for 7 days	125	Mortality	3.2% vs 5.8%	
		Placebo injection	121	Complication rate	32% vs 55.4%, p<0.005; high risk group 38% vs 65%, p<0.01; low risk group 25% and 42%, NS	
Pederzoli et al 1994[18]	MC, DB, PC, PL	Octreotide 100mcg thrice daily for 7 days	122	Complication rate	Overall -15.6% vs 229.2%, p=0.01; low-risk group p=0.05, NS in high-risk group	4 patients on octreotide - rash in 2 patients, vomiting - 1 patient, biliary sludge - 1 patient
		Placebo	130	Mortality	2 vs 5 patients	
Friess et al 1995[19]	MC, R, DB, PC	Octreotide 100mcg thrice daily for 8 days	122	Mortality	0.8% vs 0.4%, NS	
		Placebo injections	125	Complication rate	16.4% vs 29.6%, p<0.007	
Montorsi et al 1995[20]	MC, R,DB, PC	Octreotide 100mcg thrice daily for 7 days	111	Mortality	8.1% vs 5.6%	Mild gastro-intestinal
		Placebo	107	Complication rate	21.6% vs 36.4%, p<0.05	

VARICEAL HAEMORRHAGE

Ref.	Design	Patient numbers/ Intervention	Dose	Inclusion criteria	Exclusion criteria	Outcome measures	Results	Adverse events
Huang et al 1992[22]	SC, R,C	20 - Octreotide	100mcg stat, then 25 mcg/h for 24 h	Endoscopically confirmed active variceal bleeding, cirrhosis	IHD, previous shunt insertion, previous sclerotherapy, COAD, CVS, poorly controlled IDDM, renal insufficiency	Initial haemostasis	75% vs 62%-NS	
		21 - Vasopressin	0.4U/min for 24h			Complete control of bleeding within 24 hours	60% vs 33%-NS	
Hwang et al 1992[23]	R, C, O	24 - Octreotide	100mcg bolus, then 25mcg/h for 24h	Endoscopically confirmed oesophageal bleeding (patients with HCC were included), cirrhosis	Coronary artery disease, arrythmias, previous portacaval anastomosis, malignant hypertension, CVA, pregnancy, COAD	Initial control of bleeding	88% vs 54% (p=0.03)	Octreotide - 3 abdominal pain
		24 - Vasopressin	0.4U/min for 24h			Complete control of bleeding at 24h	63% vs 46% (NS)	Vasopressin- 2 headache, 4 chest pain, 5 abdominal pain
						Mortality at 42d	46% vs 50% (NS) - for those patients where bleeding was controlled in 6h Mortality was 35% vs 78% (p=0.02)	
Silvain et al 1993[24]	MC, R, O	41 - Terlipressin	2mg bolus, then 1mg 4h for 24h + nitroglycerin 10mg 12h for 24 h	Patients with cirrhosis, active oesophageal bleeding seen on endoscopy	Coronary artery disease, HCC, Severe liver failure, no active bleeding, previous bleeding in preceding 8 days	Control of bleeding within 12h	59% vs 78% (p=0.064)	Terlipressin -Major -1 LVF & death and 1 bradycardia; Minor - 2 bradycardia, 1 tachycardia, 1 hypertension
		46 - Octreotide	25mcg/h infusion for 12 h then 100mcg s/c at 12h and 18h			Transfusion requirements	Less octreotide vs terlipressin (p=0.012)	Octreotide - Major -0; Minor - 7 moderate hypoglycaemia, 2 transient diarrhoea
Sung 1995[25]	O,SC, R	47 - variceal ligation		>16y, endoscopically confirmed bleeding, or recently bleeding varices, no previous oesophageal bleed for other reasons	Previous endoscopic treatment of varices or shunt surgery, other GI bleeding, HCC	Initial success of haemostasis	NS	
		47 - variceal ligation plus octreotide	50mcg iv bolus then infusion at 50mcg/h for unstated period			Rebleeding as inpatients	38% vs 9% (p=0.0007)	
						Use of balloon tamponade	10 patients vs 1 patient (p=0.0039)	
						Blood transfusion requirement	Slightly higher in ligation only group (p=0.06)	
						Inpatient, 30d and 1y mortality	Trend to lower mortality with combined therapy, but NS	

VARICEAL HAEMORRHAGE (continued)

Ref.	Design	Patient numbers/ intervention	Dose	Inclusion criteria	Exclusion criteria	Outcome measures	Results	Adverse events
Besson et al, 1995[26]	MC, DB, R, C	All patients underwent emergency sclerotherapy then: 98 - octreotide 101 - placebo	25mcg/h for 5d	Endoscopically confirmed oesophageal bleeding or recent bleeding, cirrhosis	Previously entered into trial, bleeding varices within previous 15d if sclerotherapy had been given or 8d if balloon tamponade/vasoactive drugs had been given, severe liver failure, HCC, noncirrhotic portal hypertension, >80	Survival without rebleeding at 5d Transfusion requirements in first 24h Survival	87% vs 71% (p=0.009) Significantly lower in Gp1 (mean 1.2 units vs 2.0 units, p=0.006) At 5d, 7 vs 10 had died. At 15 days 12 in each group had died	Minor
Sung 1993[27]	O,SC, R	49 – emergency sclerotherapy 49 – octreotide infusion then elective sclerotherapy	50mcg intravenous bolus then 48h infusion at 50mcg/h	>16y, endoscopically confirmed bleeding, or recently bleeding varices, no previous oesophageal bleed for other reasons		Control of active bleeding Recurrence of haemorrhage in first 48h Use of balloon tamponade Duration of hospital stay 48h and 30d mortality	90% vs 84%(p=0.55) 16% vs 14% (p=1) NS NS NS	18 patients (37%) had s/e post sclerotherapy. 3 patients had pleural effusion and 1 patient had aspiration pneumonia 5 patients had nausea after octreotide bolus
Jenkins et al, 1997[21]	O, R, MC	73 – octreotide infusion followed by elective sclerotherapy 77 – emergency sclerotherapy	50 mcg/h for 48h	Endoscopically confirmed variceal bleed	Patients with oesophageal balloon inset, patients who had received vasoactive drugs of injection sclerotherapy in the previous seven days	Control of active bleeding in 48h Incidence of mortality at 60 days	85% vs 82%, p=NS; 18% vs 26% of patients also required up to 12h balloon tamponade to control bleeding which was not considered a treatment failure 31.5% vs 16.9%, p=NS, mostly associated with severe liver disease	19% vs 26% experienced s/e; 15 patients in the octreotide experienced hyperglycaemia requiring insulin in 2 pts, 1 pt on octreotide developed pulmonary oedema and another paralytic ileus
Primignani et al 1995[28]	MC, R, PC, DB	All patients had EVS after enrolment, unless previously treated with EVS, then randomised to: 26 – octreotide 32 - placebo Patients received EVS as necessary	100mcg s/c thrice daily to day 29	Haemodynamically stable for 24h after variceal bleeding stopped (pts treated with EVS, balloon tamponade, terlipressin or somatostatin), cirrhosis	Unstable IHD, VT, advanced HCC, other neoplasms with life expectancy <6m, IDDM, elective sclerotherapy, portosystemic shunts, <18y	Rebleeding Total number of deaths Bleeding- related death	31% vs 34% at 90d (NS) 10 vs 7 (NS) 7 vs 5	
Jenkins et al 1997[29]	SC, R,C	16 – sclerotherapy + octreotide 16 – sclerotherapy alone	50mcg bd for 6 months	Cirrhosis and variceal bleeding		Rebleeding Survival	1 patient vs 7 patients rebled (p=0.037) 0 vs 5, p<0.02	Minor

ACUTE PANCREATITIS

Reference	Design	Intervention	No. Of patients	Outcome measures	Result	Adverse events
Beechey-Newman 1993[31]	SC	Octreotide, 250mcg stat, then 0.5mcg/kg/h	9	Frequency of poor prognosis signs	After 48h the octreotide group had developed significantly fewer prognostic indicators. For full details see original paper	
		No treatment	10	Pethidine requirement	Octreotide group required less pethidine- but range was wide in both groups; median amount 520mg (122.5mg-1447mg) vs 1265mg (460mg-7003mg), p<0.05	
Paran et al 1995[32]	R, MC	Octreotide 100mcg thrice daily for 14d	19	Complication rate	26% vs 74%, p=0.004; ARDS 37% vs 63%, p=0.1	1 patient complained of pain on injection
		No treatment	19	Length of inpatient stay	17.9d vs 34.1d, p=0.02	
				Mortality	2 vs 6, p=0.11	
Fiedler et al 1996[33]	SC, CC	100mcg thrice daily for 10d	39	Mortality	26% vs 61%, p<0.01	
		Historical controls, no treatment	54	Complications	ARDS - 18% vs 40%, p<0.05; circulatory shock syndrome – 51% vs 87%, p<0.05	
McKay et al 1997[34]	MC, R, PC	Octreotide 40mcg/h for 5d	28	Mortality	18% vs 20%, NS	
		Placebo	30	Complications	15 vs 11	
					Combined mortality + morbidity rate = 54% vs 40%	

AIDS-RELATED DIARRHOEA

Reference	Design	Intervention	No. of patients	Outcome measures	Results	Adverse events
Cello et al 1991[40]	O	50 mcg - 500 mcg/24 h for 7 days on maintenance dose	51	Decrease in stool frequency	6.5 stool/day reduced to 3.8, p<0.001	Pain at injection site, nausea, cramping, bloating in some patients
				Decrease in stool volume	1604 ml/day reduced to 1084 ml/d, p<0.001	
					21 patients (41%) had a complete or partial response	
Compean et al 1994[41]	R,C	Octreotide 100 mcg-300 mcg tds for 10/7	10	Complete response	2 vs 0	8 patients on octreotide experienced s/e compared with 3 in control group.
		2mg-6mg loperamide tds + 2.5mg -7.5 mg diphenoxylate tds + placebo for 10/7	10	Partial response	4 vs 2 p<0.05	Adverse events included abdominal pain, nausea, vomiting, paresthesia and pain at site of injection
Simon et al, 1995[42]	R, PC, DB	Octreotide 100 mcg-300 mcg tds for 21/7	74	30% decrease in stool weight (at least 250ml reduction from baseline)	46% vs 36% (p=0.35)	51% vs 38% experienced adverse events. Included abdominal discomfort, fever and skin rash, nausea, vomiting, pain on injection
		Placebo for 21/7	50			

CHEMOTHERAPY-INDUCED DIARRHOEA

Reference	Design	Intervention	No. of patients	Outcome measures	Results	Adverse events
Cascinu et al, 1993[43]	R, C	Octreotide 100mcg bd for 3/7	21	Resolution of diarrhoea	19 vs 3, p<0.005	None recorded
		Loperamide 4mg stat, 2mg 6h for 3/7	20			
Gebbia et al, 1993[44]	R, C	Octreotide 500mcg tds	20	Resolution of diarrhoea within 4 days	80% vs 30%, p<0.001	Pain at site of injection (15%), mild abdominal pain (15%)
		Loperamide 4mg tds	20			
		Continued until complete remission of diarrhoea or until 4d treatment had elapsed				
Geller et al, 1995[45]	R, C	Octreotide 150mcg-2.4mg/24h	22	Major response at 48h	10 (86%) vs 12 (45%), p=0.033	Mild elevation of bilirubin (2), abdominal cramping and flatulence (1)
		Loperamide 4mg qds Continued until resolution	14			

DUMPING SYNDROME

Reference	Design	Intervention	No. of patients	Outcome measure	Results	Adverse events
Tulassay et al, 1989[51]	R, DB, PC, CO	Octreotide 50mcg pre-glucose meal Placebo Or vice versa	8	Symptom control	Reduction of symptoms in treatment group, p<0.001	Not recorded
Geer et al, 1990[50]	R, DB, PC, CO	Octreotide 100mcg pre-meal Placebo Or vice versa	10	Symptom control by severity score	1.7 vs 8.5, p<0.001	Not recorded
Gray et al 1991[52]	R, DB, PC, CO	Octreotide 100mcg pre-meal Placebo Or vice versa	9	Symptom control	2 vs 9 patients became symptomatic, p=0.004	Not recorded

ENTERIC FISTULA

Reference	Design	Intervention	No. of patients	Outcome measures	Results	Adverse events
Nubiola-Calonge et al, 1987[53]	SB, PC, CO	Octreotide 225mcg-300mcg/24h for 2d followed by placebo for 2d (group 1)	14	Reduction in fistula output/24 h	Group 1 – 498ml to 228ml, p=0.014; Group 2 - 828ml to 247ml, p<0.01	Allergic reaction (1), cholestasis (1)
		As above, vice versa (group 2)		Time to fistula closure	Mean 4.5 days in 11 patients where the fistula closed	
		Then all patients received octreotide until closure of fistula or operation				
Sancho et al 1995[54]	R, DB, PC	Octreotide 100mcg tds + TPN	14	% reduction in output	NS	Hyperglycaemia (1), pain at injection site
		Placebo + TPN	17	Rate of spontaneous closure within 20d	8/14 vs 6/17, p=NS	
		Both initiated within 8d of fistula onset				

GASTRO-INTESTINAL CANCERS

Reference	Design	Intervention	No. of patients	Outcome measures	Results	Adverse events
Cascinu et al, 1995[55]	R, O	Octreotide 200mcg tds for 5d each week + supportive care	55	Survival time	20 weeks vs 11 weeks, p<0.0001	Asymptomatic hyperglycaemia (20), mild steatorrhoea (10), abdominal cramps (3)
		Best supportive care only Continued until disease progression, toxicity or patient refusal	52	Response rate	45% vs 15% had stable disease, p<0.001	
Goldberg et al, 1995[56]	R, C	Octreotide 150 mcg tds or no treatment	Octreotide - 131	Median time to progression	3.4 months vs 3.2 months, p=0.99	Diarrhoea (44%), steatorrhoea (30%), nausea (26%)
	R, PC, DB	Octreotide 150 mcg tds or placebo	Untreated/ placebo - 129	Median survival time	17 months vs 16.8 months, p=0.77	
Kouroumalis et al, 1998[57]	R, O, SC	Octreotide 250 mcg bd until withdrawal/death	28	Median length of survival	13.0 months (95% CI 9.3 to 16.7) vs 4.0 months (95% CI 1.9 to 6.2), p=0.002	4 pts withdrew from octreotide treatment because of the need for injections
		No treatment	30			

ERCP-INDUCED PANCREATITIS

Reference	Design	Intervention	No. of patients	Outcome measure	Results	Adverse events
Binmoeller et al, 1992[36]	R, PC, DB	Octreotide 100mcg pre and post-op	121	Incidence of pancreatitis	3 vs 2, p=NS	None attributable to octreotide
		Placebo	124			
Arcidiacono et al, 1994[37]	R, PC, DB	Octreotide 100mcg pre and post-op	75	Incidence of pancreatitis	5 vs 5, p=NS	Pain and irritation at injection site (3), nausea (1)
		Placebo	76			
Sternlieb et al, 1992[38]	R, PC, DB, MC	Octreotide 100mcg pre and post-op	40	Incidence of pancreatitis	35% vs 11%, p<0.01, thus necessitating trial termination	None attributable to octreotide
		Placebo	44			
Tulassay Z et al, 1998[39]	R, PC, MC	Octreotide 100 mcg pre and post-op	599	Incidence of pancreatitis	46(5.9%) vs 48 (6%), p=NS	Blood glucose was significantly higher in the octreotide group
		Placebo	600	Rise in amylase to > twice normal limit	192 (32%) vs 216 (36%), p<0.05	

APPENDIX 3. NORTHERN AND YORKSHIRE PRESCRIBING COSTS